REMARKS

Status of the Claims

Claims 1, 13, 14, 27-45, and 55-61 are pending in the instant application. Claims 2-12, 15-26 and 46-54 have been canceled without prejudice. Claims 1 and 55-61 are currently under examination. Claims 13-14 and 27-45 have been withdrawn. Applicants reserve the right to request rejoinder of the withdrawn claims in accordance with the provisions of MPEP § 821.04.

Applicants have amended claims 1 and 13 (presently withdrawn) with this submission to draw the claims to particular preferred embodiments of the invention, specifically, R^1 is limited to phenyl, having from one to three halo substituents, R^2 is limited to hydrogen or C_1-C_3 alkyl, R^3 is limited to hydrogen or methyl, and R^4 and R^5 are each limited to hydrogen. Claim dependency in claim 55 has been corrected and new Claims 59-61 have been added to more specifically claim particular preferred embodiments of pharmaceutical formulations of the present invention.

Remarks Regarding 103

Claims 1-7 and 46-58 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Krushinski *et al.* (U.S. 6,777,428, "Krushinski") in view of King ("Medicinal chemistry: principles and practice" p. 206-209, 1994, "King"). Claims 2-7 and 46-54 have been canceled without prejudice. The rejection with respectfully to these is therefore obviated. Applicants respectfully traverse the rejection as applied to the remaining claims.

The Office Action alleges that, in view of King, substitution of the phenyl ring of the compounds disclosed by Krushinski with the pyridinyl ring of the compounds of the present application is *prima facie* obvious. However, the test for establishing the *prima facie* obviousness of similar compounds requires more than just a showing of a structural similarity of the prior art and the claimed compounds and the cited King reference does not provide such additional information or rationale. It fact the King reference teaches away from such a rationale.

The Federal Circuit in *Takeda Chemical Industries v. Alphapharm Pty.* recently discussed the test for establishing the prima facie obviousness of similar chemical compounds. 492 F.3d 1350 (Fed. Cir. 2007). Noting that their "case law concerning prima facie obviousness of structurally similar compounds is well established," the court stated:

> In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate

> support in the prior art" for the change in structure.... [I]n order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modification necessary to achieve the claimed invention" [is] also required.

Id. at 1356 (citations omitted). The court continued by saying that the above "test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in" the Supreme Court's recent decision of *KSR Int'l v. Teleflex Inc.*, 550 U.S. ____ (2007), 127 S. Ct. 1727 (2007). *Id.* Therefore, the court concluded that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Id.* at 1357 (emphasis added).

The Office Action presents no reason as to why one of ordinary skill in the art would modify the compounds of Krushinski in the "particular manner" necessary to obtain the compounds of the present invention. The secondary reference, King, is an excerpt from a general medicinal chemistry textbook, which lists a number of potential isosteric substitutions with no guidance or rationale as to why one of ordinary skill in the art would choose any one over another, much less modify the phenyl piperidine ketone compounds of Krushinski to arrive at the pyridinyl piperidine ketone compounds of the present application. Furthermore, there is no guidance as to which of the 6 available carbon atoms in the phenyl ring of Krushinski should to be replaced, noting that a carbon to nitrogen change at any one of the positions over another could have significantly different effects on the electron density of the resultant pyridine ring, resulting in significant differences in the resulting molecule's interaction with the receptor, its function, bioavailability, and/or metabolism. No reason is given, in either reference, as to why one would choose to substitute in a pyridyl nor, having done so, the particular carbon to nitrogen substitution that leads to the compounds of the present application. Because there is nothing in the prior art to suggest making the specific molecular modification from the phenyl compounds of Krushinski to the pyridyl compounds of the present application, it is respectfully asserted that a *prima facie* case of obviousness cannot be made in this case.

Furthermore, King teaches away from finding a prima facie case of obviousness here. King teaches that "[i]n general, *classical isosteric* replacement ... only becomes a *bioisosteric*

replacement if biological activity is retained." King, pg. 207 last paragraph (emphasis added). King then goes on to state:

> When considering any approach to lead optimization, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacement are no exception and this should be considered when analyzing the result of such replacements. For example a simple CH_2 to O to S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pK_a, metabolism, or hydrogen bonding capacity, all with unpredictable effects upon biological activity.

King, pg. 209, lines 1-7 (emphasis added). Rather than teaching that isosteric "modification of a proven compound with conventional skill which is expected to produce similar activity consistent with the expectation of the intended modification" as stated in the Office Action (see Office Action at page 3), King teaches that isosteric replacement is an unpredictable art and that for any particular chemical modification one would expect significant differences in properties, such as various biological activities. Thus rather than leading one of ordinary skill in the art to modify the known Krushinski compounds in the particular manner in the present case to achieve the presently claimed compounds, the King reference speaks only in generalities and makes it clear that if anything, significant differences in properties are to be expected rather than unexpected. As such, it is respectfully submitted that King is properly either inapplicable/unuseful to the present analysis or in fairness supports a finding of non-obviousness. Again, it is submitted that a *prima facie* case of obviousness has not been established and withdrawal of the rejection is kindly requested.

Finally, in an effort to facilitate the more timely allowance of the case and in spite of the lack of a *prima facie* case of obviousness that would require such a showing, a comparison of the pharmacokinetics of the elected species of the present application to the analogous compound of Krushinski, at col. 46, lines 63-65, as referenced in the Office Action, yields surprising and unexpected results. Similar data for other comparable compound pairs available at the time are also presented.

Applicants present herewith the declaration of Dr. Steven Swanson ("the Declaration") which lists comparative oral exposure data for four sets of pyridyl / phenyl compounds in Table 1. The three pairs of compounds are compounds where R^1 is halo-substituted phenyl, which matches the scope of R^1 in the presently amended Claims (Compound **A** / Compound **B**;

Compound **C** / Compound **D**; and Compound **E** / Compound **F**). The comparative data in Table 1 indicate improved oral exposure for the pyridyl compounds relative to the phenyl compounds.

The phenyl compound referred to in the Office Action is Compound **B** and the pyridyl counterpart claimed here (see, e.g., Example 21) is Compound **A**. As Dr. Swanson's declaration demonstrates, the oral exposure (AUC) and maximum plasma concentration (C_{max}) for the two compounds was compared using a standard dog study, and it was found to be dramatically and unexpectedly different. (The Declaration, ¶¶10-12.) The level of metabolism in a human liver microsome assay was also better (lower) for Compound **A** of the present invention. For the elected species of the present application, the oral exposure as measured by the area under the curve was 223 ng·hr/ml and the C_{max} was 35.6 ng/mL. By contrast, the oral exposure for the analogous compound of Krushinski, Compound **B**, was only 31 ng·hr/ml with a C_{max} of 3.9 ng/mL. The oral exposure and C_{max} of the elected species of the present application are close to an order of magnitude greater than the allegedly closest prior art compound. For 5-HT_{1F} agonists which are candidates for treating and/or preventing migraine, rapid bioavailability is an important criterion.

The data for compound pairs C/D and E/F demonstrate similar findings. Therefore, the surprising, unexpected and improved properties that have been found for the presently claimed compounds are sufficient to demonstrate the non-obviousness of the present invention.

The facts of *Takeda* (supra) also support the sufficiency of these data in regard to a finding of non-obviousness. In this case, Takeda obtained a patent (US Patent 4,687,777) relating to thiazolidinedione compounds, useful as antidiabetic agents. The claimed compound contained an ethyl-substituted pyridyl ring, where the ethyl substituent could be located at one of four different positions on the pyridine, including the 5-ethyl compound, pioglitazone. Alphapharm sought to invalidate the patent as *prima facie* obvious under 35 USC §103 in view of a compound having a methyl group at the 6-position. The Federal Circuit rejected Alphapharm's argument, because Alphapharm failed to provide evidence that the prior art compound would have been selected as the lead compound, and failed to identify a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the clamed compounds: a *prima facie* case for obviousness was not established. See *Takeda* at 1363, (e.g., the prior art document did not refer to any specific position as particularly promising, *Id.* at 1362). Separately, the Federal Circuit also rejected Alphapharm's argument

because of evidence for unexpectedly superior non-toxic properties of the claimed compounds that would have rebutted a finding of *prima facie* obviousness if the *prima facie* case had been found to be established. (*Id.* at 1361).

Applicants would also like to draw the Examiner's attention to *Ex parte Koo,* 150 USPQ 131 (1965), in which the Examiner considered it obvious for a chemist of ordinary skill in the art to substitute a pyridyl group for a phenyl group. The court disagreed, stating that "although pyridine and benzene are similar in many respects, effect of their interchange in instant complex nucleus could not be foretold." *Id.* at 131.

For the reasons stated above, Applicants assert that the claimed invention is not *prima facie* obvious over Krushinski in view of King or otherwise and that the presented data further demonstrates the non-obviousness of the present invention. Withdrawal of this rejection is respectfully requested.

Remarks Regarding Double Patenting Rejection

Claims 1-7 and 46-58 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-7 of Krushinski *et al.* (U.S. 6,777,428) alone or in view of claims 1-8 of Blanco *et al.* (US20060211734, "Blanco"). Claims 2-7 and 46-54 have been canceled without prejudice. The rejection with respectfully to these is therefore obviated. Applicants respectfully traverse the rejection as applied to the remaining claims.

For the reasons stated above, the claims of the present application are not obvious over Krushinski. The compounds of the Blanco reference are structurally more dissimilar to the presently claimed compounds than the compounds of the Krushinski reference and the same remarks regarding non-obviousness as presented above apply. Therefore, the claims of the present application are patentably distinct from the claims of Krushinski, either alone or in view of the claims of Blanco. Therefore, Applicants assert that a rejection on the ground of nonstatutory obviousness-type double patenting over the claims of Krushinski, either alone or in view of the claims of Blanco, is not appropriate and respectfully request the withdrawal of this rejection.

CONCLUSION

Applicants believe that all objections and rejections have been properly obviated or traversed. Favorable action on the merits is respectfully requested. If there are any questions regarding this Response, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Applicants believe no further fee is due at this time; however, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. **50-0311**, Reference Number: **34251-502 NATL** (Customer Number: **30623**).

Respectfully submitted,

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